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(54) Titre : PREPARATION MEDICAMENTEUSE PLATE POUR ADMINISTRER OU LIBERER, DANS LA CAVITE BUCCALE, DE LA BUPRENORPHINE OU UNE SUBSTANCE COMPARABLE SUR LE PLAN PHARMACOLOGIQUE ET PROCEDE PERMETTANT DE LA PREPARER

(54) Title: FLAT MEDICAMENT PREPARATION FOR THE APPLICATION AND RELEASE OF BUPRENORPHINE OR A PHARMACOLOGICALLY COMPARABLE SUBSTANCE IN THE BUCCAL CAVITY, AND METHOD OF PRODUCING THE SAME

(57) Abrégé/Abstract:
A solid pharmaceutical preparation, disintegratable in aqueous media, with a flat, foil-shaped, paper-shaped or wafer-shaped administration form, for application and release of active substances in the oral cavity is characterized by a content of buprenorphine, of an active substance pharmacologically comparable to buprenorphine, or of a therapeutically suitable salt of buprenorphine or the pharmacologically comparable active substance.

ABSTRACT

A solid pharmaceutical preparation, disintegratable in aqueous media, with a flat, foil-shaped, paper-shaped or wafer-shaped administration form, for application and release of activa substances in the oral cavity is characterized by a content of buprenorphine, of an active substance pharmacologically comparable to buprenorphine, or of a therapeutically suitable salt of bruprenorphine or the pharmacologically comparable active substance.

Flat pharmaceutical preparation for application and release of buprenorphine or of a pharmacologically comparable substance in the oral cavity, and process for the production thereof

The present invention relates to a pharmaceutical preparation for application of buprenorphine or pharmacologically comparable active substances in the region of the oral cavity, respectively the oral mucosa. More particularly, it relates to a preparation that is adapted to be flat and in the form of a foil-, paper- or wafer-shaped administration form.

Flat active substance carriers have already been developed and produced for various purposes. DE-OS 27 46 414 can be regarded as fundamental to this administration form, said document describing a foil-type tape of active substance, binder and further active substances, with a direct relation existing, by reason of the homogeneous thickness, density and width, between a unit of length of the tape and the dose of active substance contained therein. The advantages of the continuous dosage property have been recognized also by other applicants and have been described in specific individual variants. Thus, DE-PS 36 30 603 claims a flat-shaped carrier material, for example in the form of a separating layer, with an active substance-containing coating, the latter being peelable, in doses, off the carrier material after having been previously separated into dosage units.

The practicability of the flat format in general and the advantages afforded in the manufacture of the administration form and in the dosing when employing such administration form have been recognized in the prior art.

Moreover, further advantages of such administration forms can be derived such as the fact that, relative to the weight of the administration form, a relatively large surface may be printed on the said administration form, thereby making it possible to increase intake safety, as well as affording the possibility of discrete intake without any liquid being available.

Despite these obvious advantages, such flat administration forms have hitherto hardly been successful. Obviously, the advantage as compared to conventional administration forms does not suffice for many manufacturers of pharmaceutics to develop products of this type comprising the usual active ingredients and to pursue the legal drug approval thereof. Moreover, existing production machinery and existing know-how cannot be made use of for these novel products; this means that the necessity of large investments would arise. Despite the above-described advantages of flat, film- or paper-like administration forms, the therapeutic and/or economic advantage in administration of common active substances which are also perorally applicable is apparently not great enough as compared to conventional tablets to justify the costs of switching over to these administration forms.

One of the substances that are little suitable for peroral administration is buprenorphine, an opiate which has been successfully used in the therapy of pain for years. After peroral application it is hardly bioavalable, i.e. it appears in the blood circulation only to the very small extent of a few percent of the dose taken (McQuay & Moore, in: Bupenorphine, ed. Cowan & Lewis, New York 1995). Presumably, the reason for the lack in bioavailability lies in the extensive decomposition of the substance during the first liver passage following gastrointestinal absorption ("first-pass effect"). A possibility of avoiding the first-

pass effect in oral administration is to bring the active substance to absorption already on the oral mucosa. In order to enter the central systemic circulation, an active substance which enters into the blood via the oral mucosa does not have to first pass the portal system and thus, in concentrated form, the liver, which metabolizes the active substance. A prerequisite for buccal or sublingual application, however, is a sufficient permeability of the oral mucosa to the active substance, taking into consideration the required dose. Permeability in turn depends to a large extent on the physicochemical properties of the active substance. Since buprenorphine is effective in very small doses, and since it has the required physicochemical characteristics, buccal or sublingual application is very attractive.

In fact, apart from injectable administration forms there are - at least in Germany - no commercially available peroral administration forms, but only so-called sublingual tablets, which comprise buprenorphine (Temgesic® sub-lingual). It is true that such tablets take into account the fact that sublingual application of the active substance is preferable to peroral administration - even though they do so above all by way of their intake directions as only these suggest the sublingual administration, not the tablet itself. However, they offer a vehicle which has considerable drawbacks for this purpose of application. Among these disadvantages is, firstly, the not inconsiderable disintegration time, which in the case of pressed tablets is at least several minutes even under favorable conditions, and in the case of the commercially available tablets is typically about 5 to 10 minutes. For patients suffering from severe, acute pain this disintegration time results in an unwanted delay of the onset of action; in a substitution or withdrawal therapy, however, this puts a strain on the medicinal personnel with

respect to the time required for administration, since the personnel must supervise that the tablets are used as directed and must prevent improper removal of the non-disintegrated tablet from the mouth. Further disadvantages of the tablet are the foreign body sensation occurring during the disintegration time, but also the great variability in the extent of sublingual absorption, which is caused by the active substance during or after disintegration of the tablet having for the most part no direct contact with the oral mucosa, but being released into the saliva; the saliva, however, can be retained in the oral cavity for a very variable time, which is more or less haphazard, before being swallowed.

It is thus the object of the present invention to create pharmaceutical preparations based on, and having the general advantages of, flat, film-like or paper-like active substance carriers which by reason of the combination with a special active substance have additional economical and/or therapeutical advantages, apart from those mentioned above, over pharmaceutical preparations of the same active substance based on conventional administration forms such as tablets. In addition, it is likewise an object of the invention to provide an administration form for buprenorphine that releases the active substance in the oral cavity while not having the disadvantages described in the prior art.

In one embodiment, the present invention provides a buccal pharmaceutical preparation for treating acute conditions of pain or for addiction therapy, comprising as active substance buprenorphine or a pharmacologically comparable substance as such or as a therapeutically suitable salt, characterized by a wafer-shaped administration form, disintegratable in the aqueous medium of the oral cavity, which has a mucoadhesive, active substance containing layer based on water-soluble, film-forming polymers of small thickness, for rapid active substance transfer through short diffusion paths, while having a large surface appropriate to the effective dose.

The object is achieved in accordance with the features of the claims by providing an administration form on the basis of a flat, foil-, paper- or wafer-like active substance carrier, which administration form contains as active substance buprenorphine, respectively one of its therapeutically acceptable salts, or a therapeutically comparable active substance. As will be explained in the following, the administration form of the present invention is by far superior to a conventional administration form for administering buprenorphine - both from the economical as well as the therapeutical point of view - and it is especially suitable, on the one hand, for analgesia in cases of acute conditions of pain, and, on the other hand, for the therapy of opiate or cocaine addiction in the sense of a substitution therapy or a withdrawal program.

The pharmaceutical preparation of the present invention can, upon application, be brought into direct contact with the oral mucosa. Due to the flat design, immediately after application about half of the surface of the administration form, which is large anyway, is located directly on the mucosa. The buprenorphine released thus encounters two factors particularly favorable for entry into the body, namely a short diffusion path and a large diffusion area. This reduces the portion of buprenorphine that is swallowed, which in the case of many other active agents would not be a particular problem. However, with buprenorphine, swallowing of the active substance should be avoided if possible, or should be reduced since, for the above mentioned reasons, swallowed buprenorphine is ineffective. Even in the case of the most simple embodiment according to the invention, and given a disintegration time of a few minutes following application or following introduction into aqueous media, the superiority of a buprenorphine-containing film over a buprenorphine-containing tablet will thus become evident.

An improved contact of the pharmaceutical preparation with the oral mucosa can be achieved through selecting auxiliary substances. It is known of certain orally applicable auxiliary agents which are commonly used in pharmaceutics that they have mucoadhesive properties. Examples for such mucoadhesive substances are polyacrylic acid, carboxy-methylcellulose, tragacanth, alginic acid, gelatin,

hydroxymethylcellulose, methylcellulose and gum arabic. In addition, it is known of various non-mucoadhesive substances that in certain mixing ratios they develop mucoadhesive properties too. An example for such a mixture is glycerol monooleate/water in a ratio of 84:16 (Engström et al., Pharm. Tech. Eur. 7 [1995], No. 2, pages 14-17).

In the case that mucoadhesive auxiliary substances are used, it is preferable for the administration form of the pharmaceutical preparation according to the invention to have a two-layer or multi-layer structure. It can thereby be prevented that the preparation conglutinates various parts of the mucosa with each other, which would lead to sensations of considerable discomfort during application. In addition, it is in such a case preferable for the administration form to have a structure the non-mucoadhesive layer of which has a permeability to the active substance which is relatively smaller than that of the mucoadhesive layer, it thereby being possible to prevent that active substance losses occur due to active substance being released into the saliva instead of to the mucosa.

Pharmaceutical preparations according to the present invention are also those containing, apart from the active substance buprenorphine or an active substance pharmacologically comparable thereto, one or more further active substances. Such a preparation can be advantageous in several respects. On the one hand it is a recognized method for treating several symptoms or conditions occurring simultaneously to administer a fixed active substance combination in a medicament. To this end, it is possible to incorporate any therapeutically appropriate active substances into the preparation according to the present invention. On the other hand, the combination, as according to the invention, of an opiate active substance

with another substance that is capable of reducing the specific risks of opiate administration is especially useful and advantageous.
Thus - possibly partial - opiate antagonists, such as, for example, nalbuphine, naloxone or naltrexone, can be combined with the opiate active substance, which results in the risk of addiction or habituation involved in the repeated administration of the preparation being diminished by reason of the fact that the dose cannot be increased without at the same time accepting an increase of the antagonistic effect. The success of this strategy will depend on the selection of a suitable antagonist as well as the selection of the dose ratio.

Though buprenorphine - optionally in the form of one of its therapeutically acceptable salts - is the most preferred active substance, the invention also relates to such active substances as are pharmacologically similar or comparable to buprenorphine since the advantages of the invention described herein also apply in these cases, though to different extent. Further suitable active substances, which are also described herein as being "pharmacologically similar or comparable", are, in particular, those substances belonging to the opiates or opioids since many of these not only exhibit pharmacodynamic but also pharmacokinetic similarities to buprenorphine, that is a relatively low dose, good capacity for permeating membranes, and a high first-pass effect. Particularly preferred are morphine derivatives or dihydromorphine derivatives as well as substances from the methadone and fentanyl group.

In order not to promote any improper application or one that does not conform to the intended use, pharmaceutical preparations according to the invention will typically be present predivided into doses and separated from each other

in a suitable package, so that when removing a dosage unit it will be possible to remove only one unit at a time, such as in the case of a blister pack, where each dosage unit is sealed individually in a deep-drawn cup. Within programs for treatment of opiate or cocaine addiction it may, however, also be useful to supply physicians who are providing the medical care, for example, with preparations in the form of packaging units wherein said preparations are present as undivided sheet-like or tape-like material, from which the dosage units can be separated for the purpose of application. This facilitates mass application and affords the physicians who are administering the preparations the possibility of separating from one and the same material various dosage units in accordance with the given dosage requirements.

Since the pharmaceutical preparation according to the present invention is expected to exhibit increased bio-availability as compared to known preparations, it will possibly be necessary to adjust the dosage. In the case of buprenorphine the individual analgesic dose will be about 0.1 to 1 mg; in addiction or substitution therapy, however, this value might be considerably higher.
In accordance with the invention the manufacture of the pharmaceutical preparation is performed in several steps. For preparing the web-shaped starting material - from which ultimately either individual doses or entire packaging units will be separated by cutting or punching - two basic process variants are suitable. The first group of processes includes those where a tape, or a process sheet or foil, is evenly coated with aqueous or solvent-containing liquids being in part of higher viscosity, and where this is subsequently subjected to a drying process. To this end, first, a coating mass is prepared, for which purpose at least one water-soluble polymer capable of forming a film, the active substance(s) and a suitable, vaporizable liquid

must be intimately mixed. If required it is possible to incorporate further auxiliary substances such as disintegration-modifying polymers, softeners, fillers, texture-providing substances, pigments, dyes, taste corrigents, solubilizers, substances for adjusting the pH, *smoothing agents, dulling agents, disintegration promoters, etc. As an alternative, the web-like starting material may be made by thermoplastic forming, i.e. without the aid of liquids. Suitable processes are, inter alia, any hot-melt coating methods as well as any extrusion methods. As a prerequisite, the polymer or polymer mixture capable of film-formation must in this case be thermoplastically formable. The required ingredients are mixed and, under action of pressure and/or heat, formed by extruding, blowing or by coating of tapes, sheets or foils, and, after solidification, transferred for further processing. Suitable for the manufacture of preparations according to the present invention that have a multi-layer structure are correspondingly modified methods, it being irrelevant whether several web-shaped materials are simultaneously or subsequently produced and combined.

New Claims

1. A buccal pharmaceutical preparation for treating acute conditions of pain or for addiction therapy, comprising as active substance buprenorphine, morphine, dihydromorphine derivatives, substances from the methadone or fentanyl groups as such or a therapeutically suitable salt thereof, characterized by a wafer-shaped administration form, disintegratable in the aqueous medium of the oral cavity, which has a mucoadhesive, active substance-containing layer based on water-soluble, film-forming polymers, for rapid active substance transfer through short diffusion paths, while having a large surface appropriate to an effective dose, the said administration form having a non-mucoadhesive outer layer, opposed to the mucoadhesive surface, which outer layer has a lower permeability to the active substance.

2. The pharmaceutical preparation according to claim 1, characterized by a two- or multi-layered structure having a mucoadhesive active substance-containing layer based on water-soluble, film-forming polymers for rapid active substance uptake through short diffusion paths.

3. The pharmaceutical preparation according to claim 1 or 2, characterized by a single-dose buprenorphine content of 0.1-1 mg.

4. The pharmaceutical preparation according to any one of claims 1 to 3, characterized in that it is equipped with bioadhesive or mucoadhesive properties by the addition of an adhesionpromoting auxiliary substance or auxiliary substance mixture.

5. The pharmaceutical preparation according to claim 4, characterized in that as a further active substance an opiate or a partial opiate antagonist is present.

6. The pharmaceutical preparation according to claim 5, characterized in that the further active substance is selected from the group consisting of nalbuphine, naloxone or naltrexone.

7. The pharmaceutical preparation according to any one of claims 1 to 6, characterized in that it is present as an undivided, sheet-shaped or tape-shaped material, from which it is possible to separate dosage units for the purpose of application.

8. The pharmaceutical preparation according to any one of claims 1 to 7, characterized in that it is present predivided into doses.

9. The pharmaceutical preparation according to any one of claims 1 to 8, characterized in that, per dosage unit, it has a content of active substance which is suitable for analgesia.

10. The pharmaceutical preparation according to any one of claims 1 to 9, characterized in that, per dosage unit, it has a content of active substance which is suitable for opiate or cocaine substitution therapy.

11. A method of producing a pharmaceutical preparation according to any one of claims 1 to 10, characterized in that in a first step at least one active substance, together with a water-soluble polymer capable of film-formation, is dissolved in a suitable, hydrophilic solvent, optionally in presence of further dissolved or suspended auxiliary agents, that in a second step the solution or suspension is applied, in a continuous process and with even thickness, to a tape or a process sheet or foil, where, in a third step, it is largely freed from the solvent, thereby forming a sheet-shaped or tape-shaped starting material, wherefrom, in a forth step, the dosage or multidosage units are separated by cutting or punching.

12. A method of producing a pharmaceutical preparation according to any one of claims 1 to 10, characterized in that in a first step at least one active substance, together with a water-soluble, thermoplastic polymer capable of film-formation, is formed, under action of heat and/or pressure, and optionally in presence of further auxiliary substances, into a sheet-shaped or tape-shaped starting material, from which starting material the dosage or multidosage units are separated by cutting or punching.

13. The method of producing a pharmaceutical preparation according to claim 11 or 12, characterized in that a plurality of simultaneously or subsequently prepared, sheet-shaped

or tape-shaped starting materials are combined to form a multilayered material, from which the dosage or multidosage units are separated.